Alcohol: Pharmacology and Neurobiology

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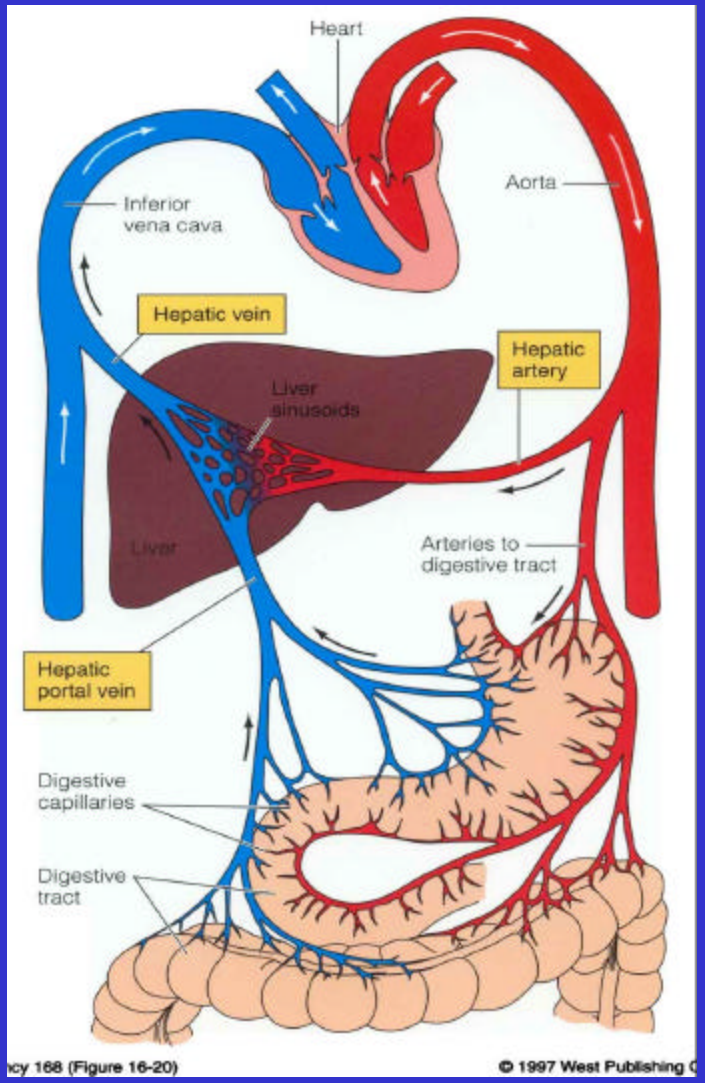
Outline

- **Pharmacokinetics: How EtOH enters, move in, & leaves**
  - **Absorption**
  - **Distribution**
  - **Metabolism**
- **Pharmacodynamics: How EtOH affects tissues**
  - **Brain [CNS]/neuropharmacological effects**
  - **Tolerance**
  - **Drugs as reinforcers of behavior, e.g., drug-taking activity**
  - **Other organ effects**

Pharmacokinetics: Absorption

- **Rapidly absorbed in stomach & upper small intestine [duodenum]**
- **Rate of absorption extremely variable**
- **Peak blood alcohol concentration (BAC) depends on:**
  - **Amount, type, & alcohol concentration of beverage**
  - **Drinking rate**
  - **Food consumption and composition**
  - **Stomach [gastric] emptying [and gastric metabolism], as upper small intestine is EtOH absorption site**
  - **Initial breakdown of alcohol in stomach & liver [first pass]**

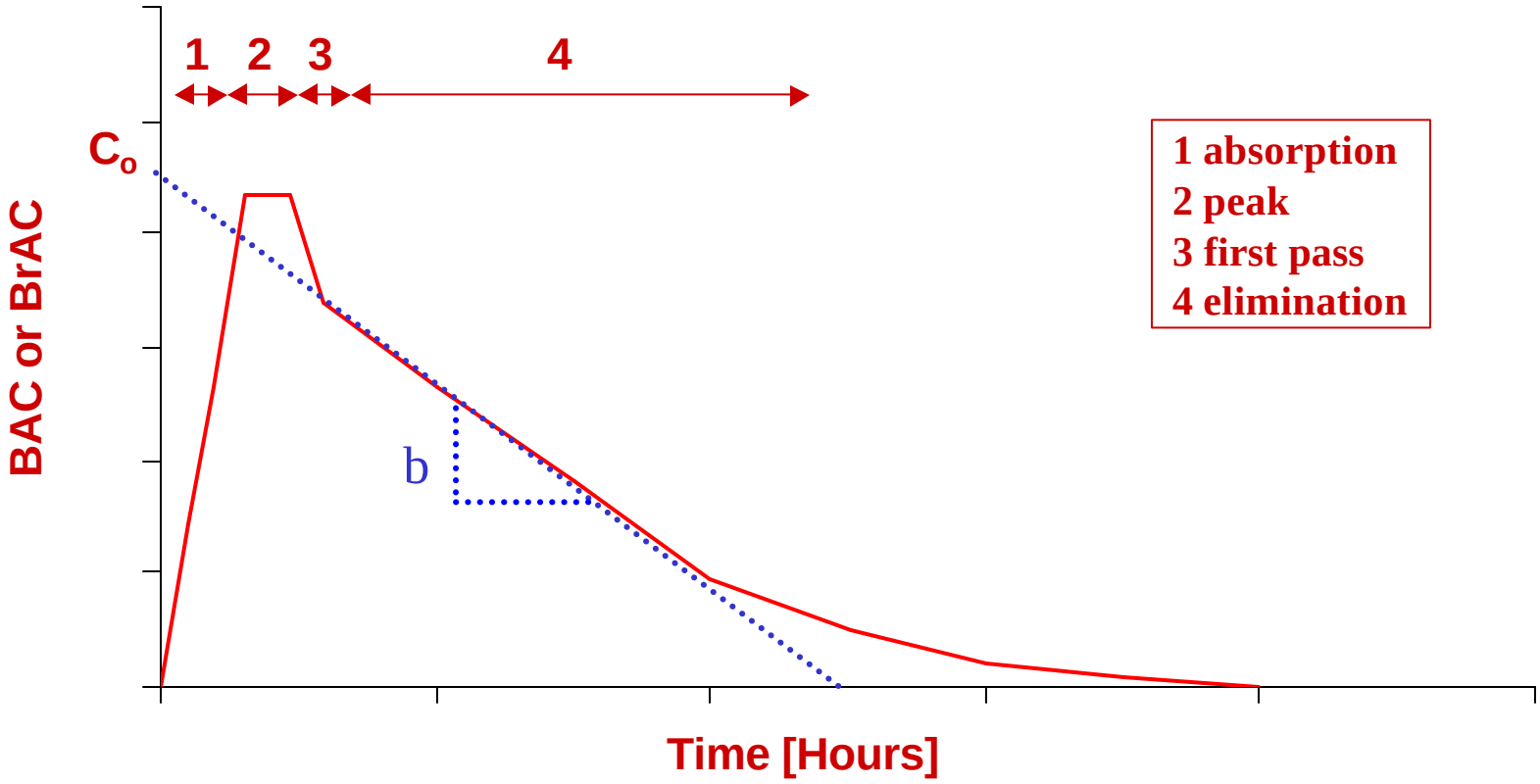
WHY DO BEER AND BRATS MAKE SUCH A GREAT TEAM?



Fatty foods are best at delaying th emptying of the stomach (enterogastric reflex)

<u>Always eat before/during alcohol consumption!</u>

Kinetics of Ethanol Concentration After a Single Dose



Distribution of Ethanol in the Body

- At equilibrium, tissue EtOH concentration depends on tissue water content.
- The rate of equilibration of ethanol in blood and a tissue depends on
  - Permeability (water content)
  - Rate of blood flow
  - Mass of the tissue
- Ethanol is practically insoluble in fats and oils
- Like water, EtOH passes readily through cell membranes.
- Ethanol distributes from the blood into all tissues and fluids in proportion to their relative content of water. Total body water is about 70%.
- Because total body fat increased in women and elderly, BAC higher
- Unlike many drugs, there is no blood plasma protein that binds EtOH.

Why is Understanding Pathways of Ethanol Metabolism Important?

- Learn how the body disposes of ethanol and its metabolites.
- Learn about factors influencing this process.
- Learn how ethanol influences the metabolism of nutrients and drugs, and affects the effectiveness of medications.
- May learn how ethanol damages various organs.
- May help to identify individuals who are at increased or decreased risk for alcohol toxicity.

Metabolism

- **Metabolism**
  - **2-10% metabolism by alcohol dehydrogenase in stomach**
  - **90-98% metabolized [broken down] in liver, principally as**

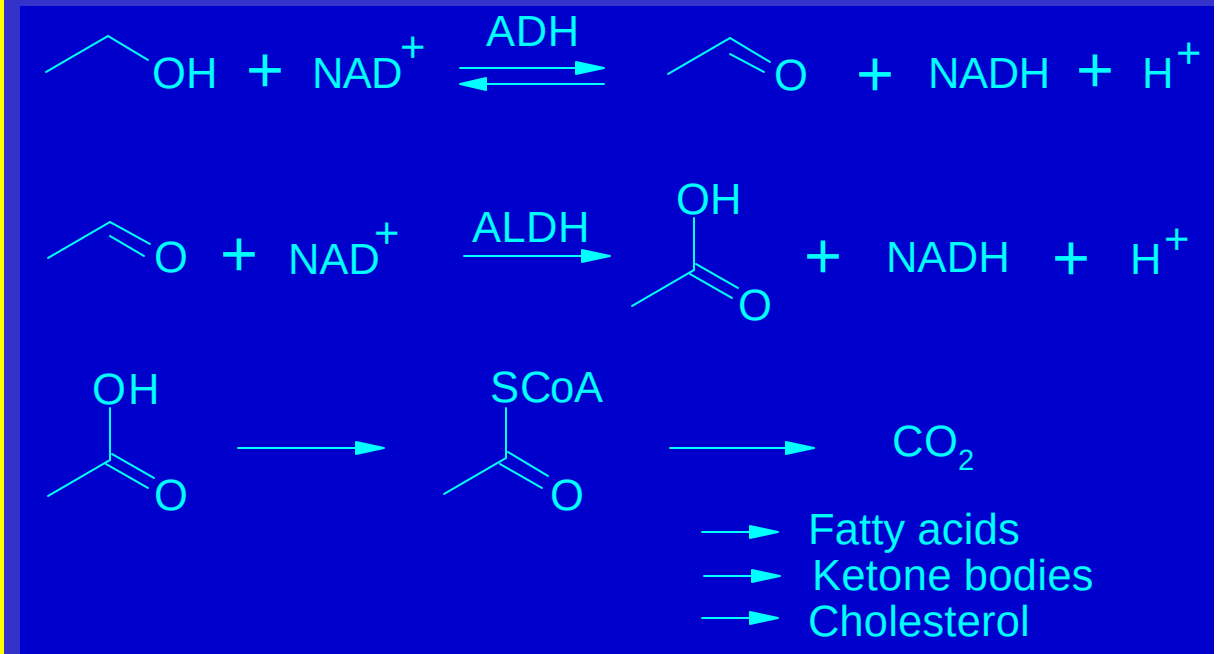
Alcohol $\xrightarrow[\text{dehydrogenase}\ \text{ADH}]{\text{Alcohol}}$ **Acetaldehyde** $\xrightarrow[\text{dehydrogenase}\ \text{ALDH}]{\text{Aldehyde}}$ **Acetate**

  - **Other paths: catalase and [inducable] p450 [cyp2E1]**
  - **Alcohol dehydrogenase saturates at low to moderate BACs**
  - **Apparent linear elimination [zero-order kinetics] rate at moderate BACs after single dose in non-chronic drinkers**
    - **Alcohol Elimination Rate = 7 g per hr [1 std. Drink = 10-15 g]**
    - **Disappearance Rate = 0.015% per hr**

General Scheme for Ethanol Oxidation

1. **< 10 % ethanol excreted in breath, sweat and urine.**
2. **~ 90 % ethanol removed by oxidation.**
3. **90+% of this ethanol oxidation occurs in the liver; remainder in stomach.**
4. **Ethanol cannot be stored in the liver.**
5. **No major feedback mechanisms to pace the rate of ethanol metabolism to the physiological conditions of the liver cell.**

ADH= Alcohol dehydrogenase
ALDH = Aldehyde dehydrogenase



Excessive NADH due to EtOH can lead to excessive buildup of fatty acids & fatty liver

Metabolism

- Metabolism

  - Aldehyde dehydrogenase usually not rate-limiting
  - Accumulation of acetaldehyde associated with headache, gastritis, nausea, dizziness (hangover)
  - Aldehyde dehydrogenase inhibition (disulfiram)

ASPIRIN BEFORE BED;

A. PREVENTATIVE MEDICINE, OR

B. COUP DE GRACE?

1. It inhibits alcohol dehydrogenase, increasing BAC

2. Inhibits blood clotting (like alcohol), which increases bleeding likelihood (hemorrhagic stroke, etc).

3. Acetylsalicylic ACID, combined with alcohol (more acid still) = ULCER RISK

4. Tylenol? (increased liver damage)

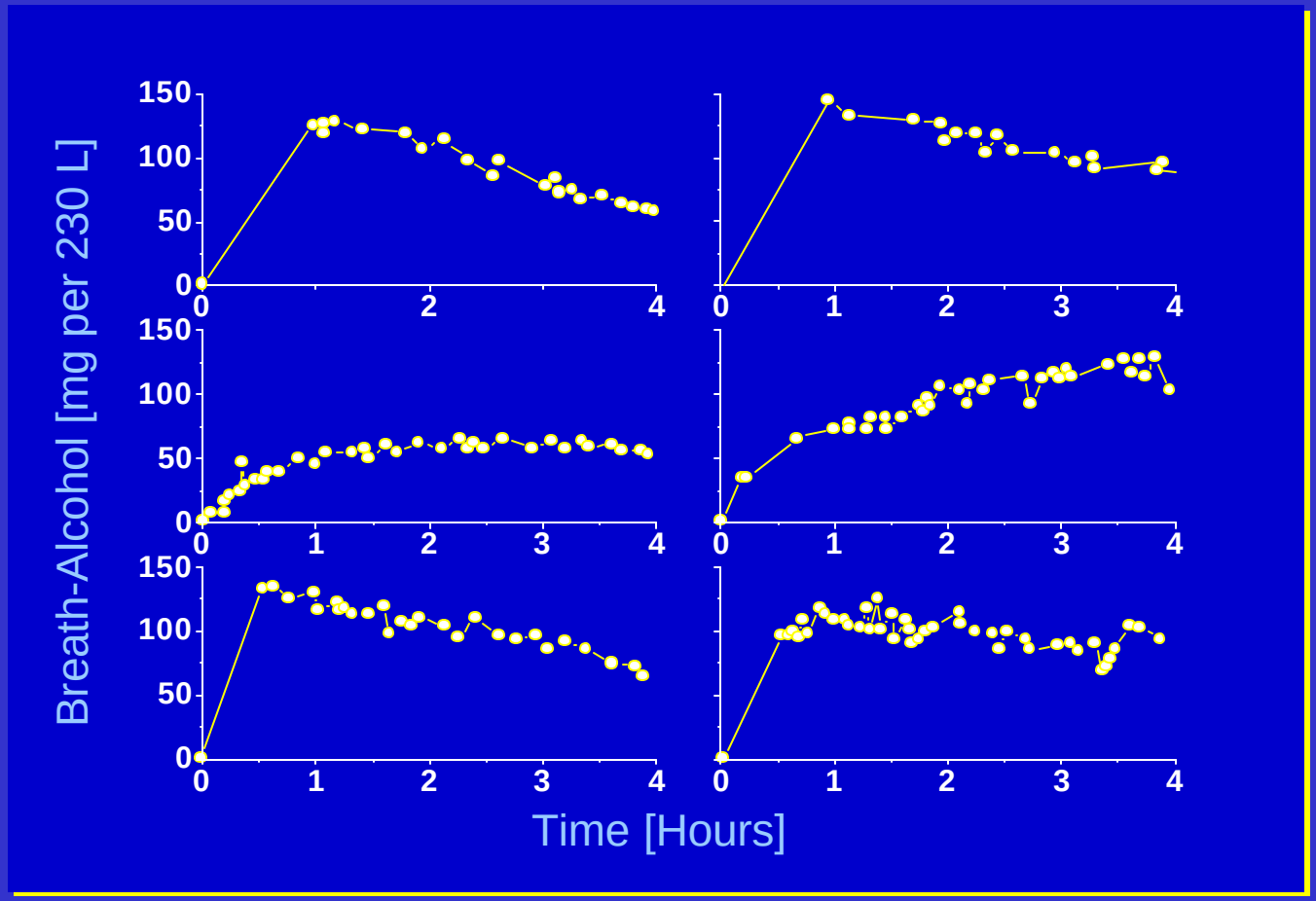
Alcohol-Drug Interactions:
The CYP2E1 system can explain

- Increased sensitivity of active drinkers to certain drugs.
- Resistance of alcoholics, in the absence of ethanol, to certain drugs.
- Increased toxicity of certain chemicals in alcoholics.
- Ethanol-dependent oxidative stress.

Factors Modifying the Ethanol Elimination Rate

There is a 3-4 fold variability in the rate of ethanol elimination by humans because of genetic and environmental factors, including sex, age, race, food, biological rhythms, exercise, alcoholism, and drugs.

Breath Alcohol Levels



Metabolism: Genetic Variation

Genetic variation in alcohol metabolizing enzymes

- **Alcohol Dehydrogenase (ADH)**
  - **Polymorphism occurs at ADH2 and ADH3 loci**

	ADH2*1	ADH2*2	ADH2*3	ADH3*1	ADH3*2
White American	95%	<5%	<5%	50%	50%
Black American	85%	<5%	15%	85%	15%
Asian	15%	85%	<5%	95%	5%

  - **15% of Black Americans have ADH2*3 allele → increased alcohol metabolic rate**

Metabolism: Genetic Variation

Genetic variation in alcohol metabolizing enzymes

- **Aldehyde Dehydrogenase (ALDH)**
  - **Genetic variation [polymorphism] at the ALDH2 gene**
    - **50% of Asians have ALDH2*2 allele**

      → decreased elimination of acetaldehyde (& alcohol)

      → flushing response after alcohol exposure
    - **Accounts for low rate of alcoholism in these populations**

Pharmacokinetics: Gender Differences

- Gender Differences
  - in absorption
    - Differences in gastric ADH activity : MALE > FEMALE
  - in volume of distribution
    - Differences in body composition and total body water (TBW)
  - in metabolism
    - Differences in liver volume, hepatic ADH activity?
- Effect of menstrual cycle on alcohol pharmacokinetics

Metabolic Adaptation (Tolerance)

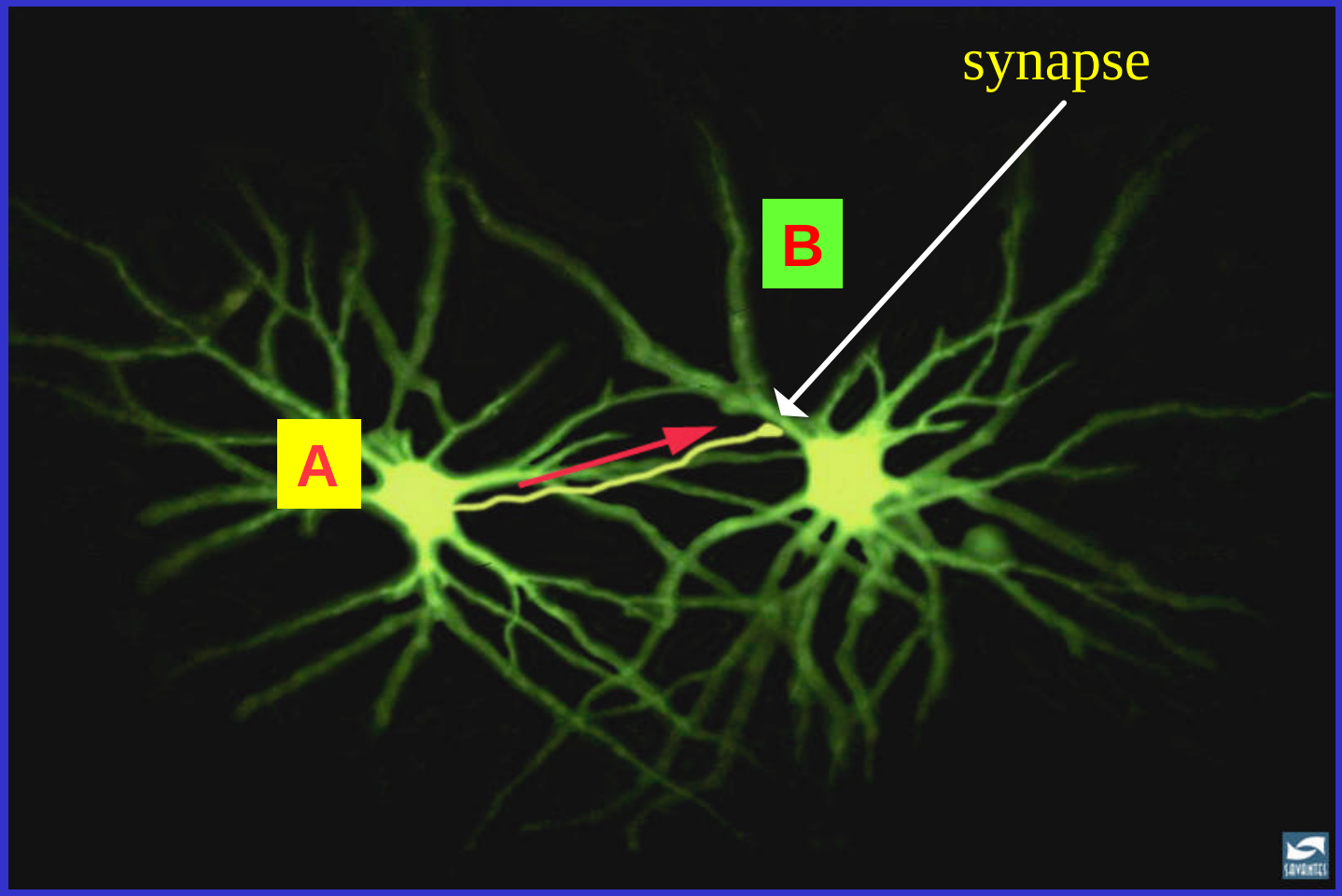
- Most tolerance increase over time is due to CNS adaptation
- Some a alcoholics (in the absence of liver disease) often display an increased rate of blood alcohol clearance. This is called metabolic tolerance or adaptation.
- Suggested mechanisms include:
    1. Increased activity [induction] of ADH.
    2. Increased ability to reoxidize NADH
    3. Induction of CYP2E1.
    4. Release of chemicals [cytokines or prostaglandins] which increase oxygen consumption by the hepatocytes. Prostaglandin inhibition by aspirin has opposite effect, raising BACs.

Why do we need to understand the cellular mechanism of ethanol action on the brain?

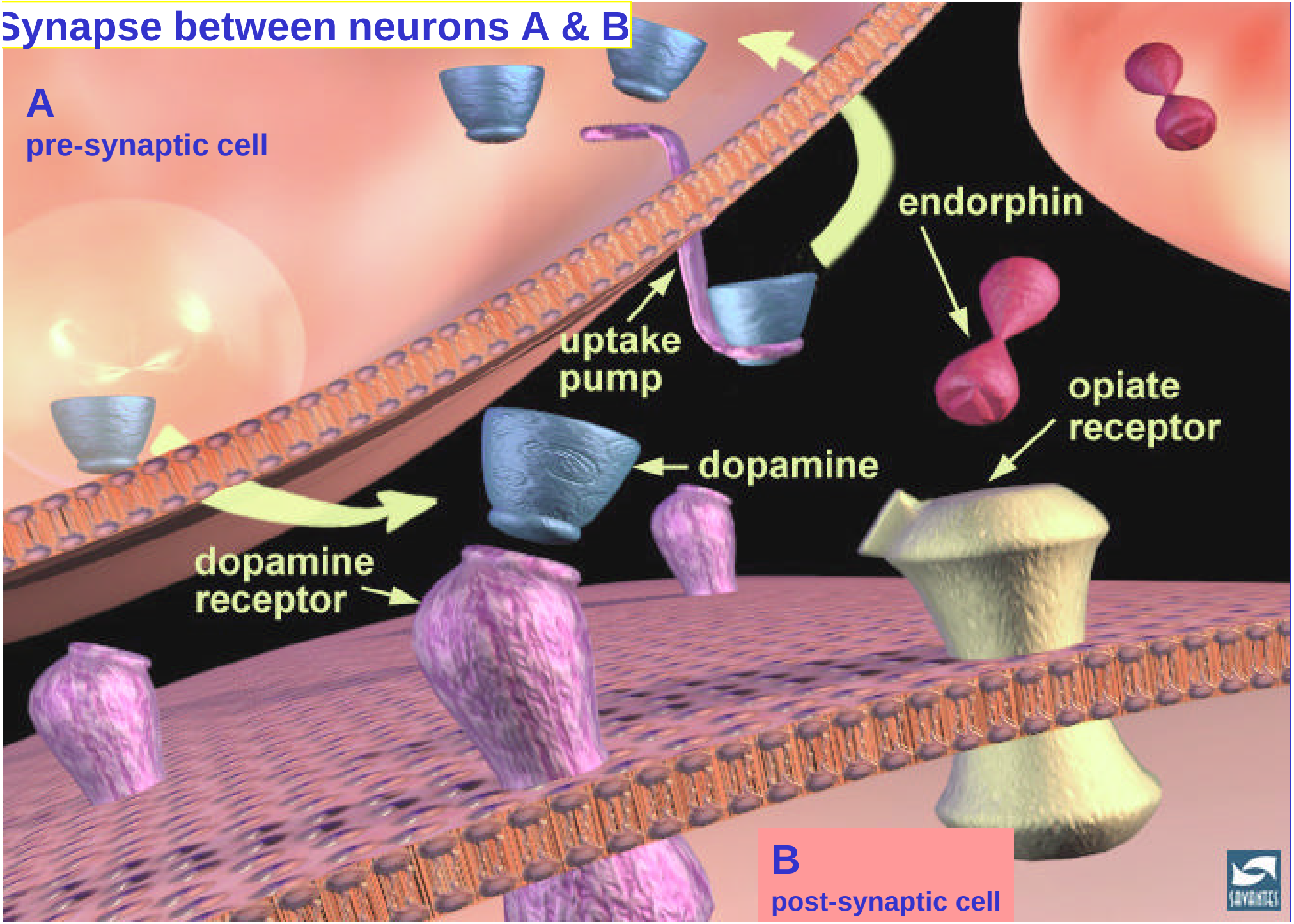
Understanding how ethanol acts on the brain at the cellular level may give insights into:

- Alcohol-related cognitive impairments and behaviors
- Pharmacological ways of antagonizing ethanol's intoxicating effects
- Pharmacological antagonism of ethanol's reinforcing effects
- Pharmacological enhancement of ethanol's aversive effects

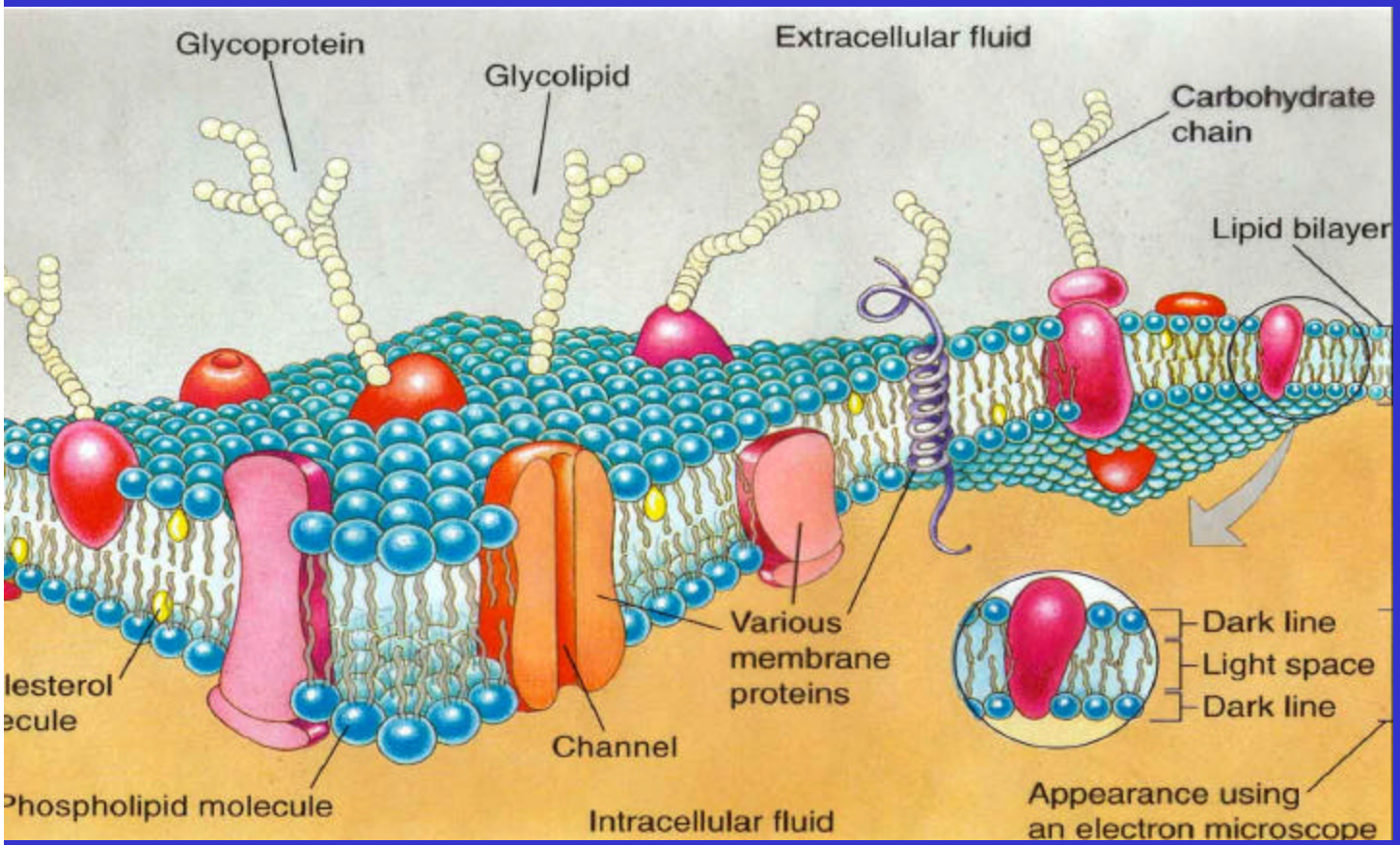
Neurons communicate in networks via synaptic connections



Synapse between neurons A & B



Proteins are the machinery that determine the function of different cell types; they're found floating free and within the membrane…..



Ion channels
(Na+, K+, Ca+2)

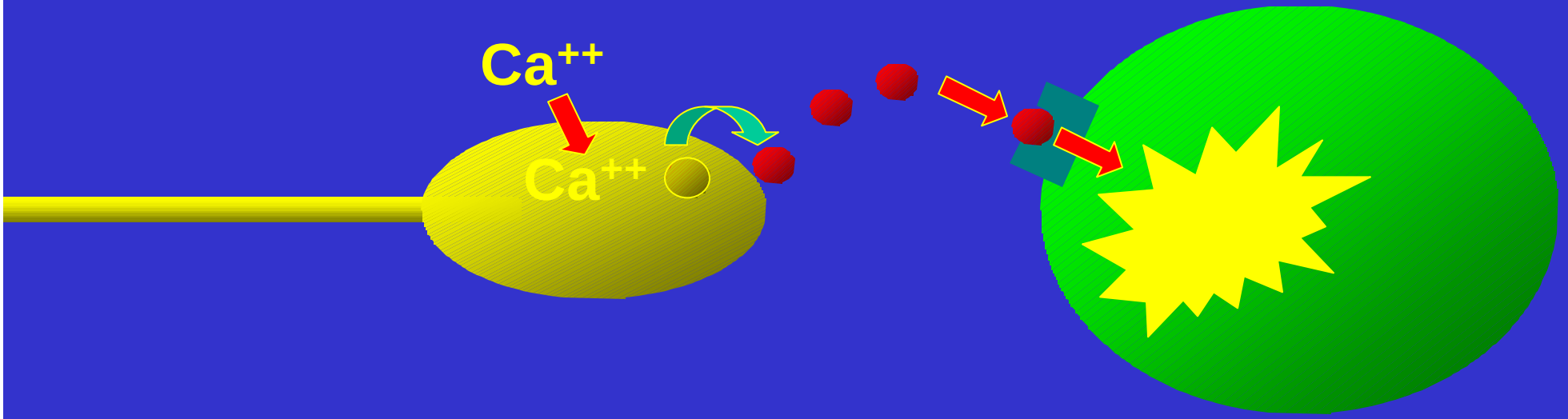
Enzymes

Signals

Receptors

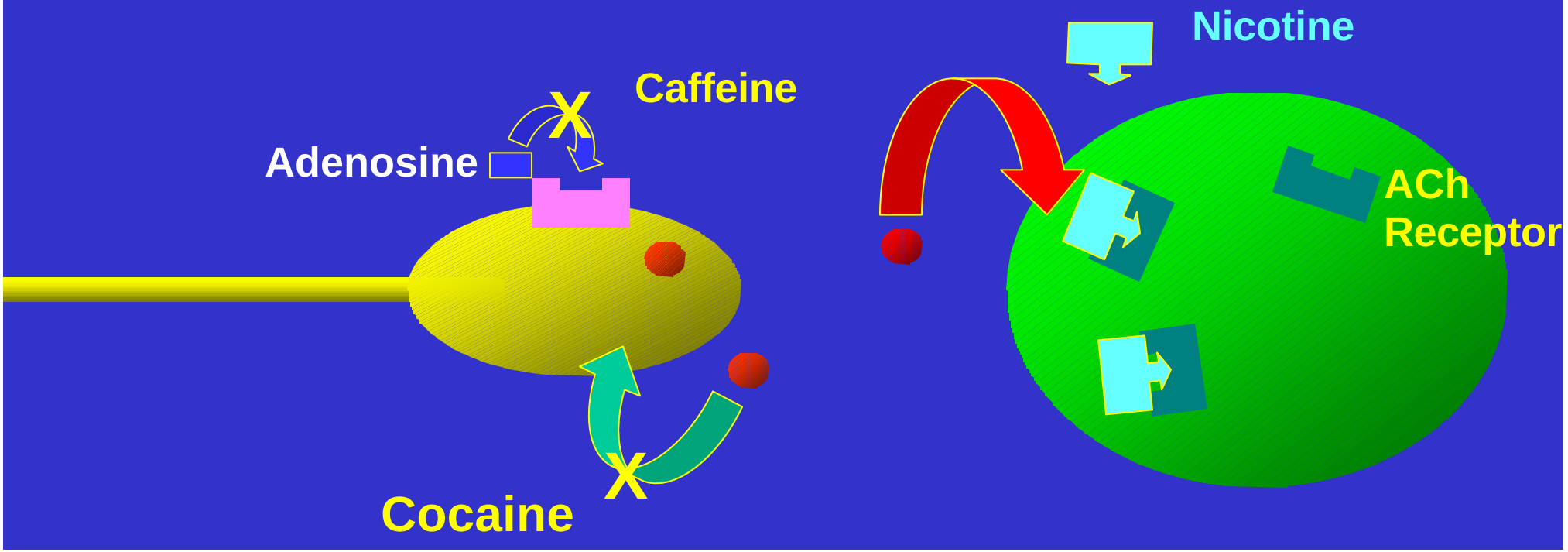
Key steps in neurotransmission:

- Synthesis and storage of neurotransmitter chemical
- Ca^{2+} dependent release upon stimulation
- Activation of postsynaptic receptors
- Transmitter inactivation by reuptake or metabolism



Synapses are major targets of neuroactive drugs

- Caffeine: inhibits adenosine receptors
- Nicotine: activates acetylcholine receptors
- Cocaine: inhibits uptake of DA, NE, 5HT
- *Ethanol: No specific receptor*



Synaptic proteins are also the targets of therapeutic drugs

- Antidepressant drugs
  serotonin uptake inhibitors
- Analgesics (morphine)
  opiate receptor agonists
- Antipsychotic drugs
  DA receptor antagonists
- Anticonvulsant drugs
  $GABA_A$ modulators
- Antianxiety agents
  $GABA_A$ modulators

Pharmacodynamics: CNS Effects

- **At various doses, alcohol is BOTH a CNS depressant and a CNS activator with many locations of action**
- **Apparent stimulatory effects result from depression of inhibitory control mechanisms in the motor systems and reinforcement centers of the brain**
- **Characteristic response:**
- **Low dose: euphoria, increased physical activity**
- **High dose: impaired coordination of movement, impaired inhibiiton of movement, impaired planning and thought processes, decreased mechanical efficiency**

Concentration-Effect Relationship

BAC [%]	Effects
0.02-0.03	Mood elevation. Slight muscle relaxation. Increased movement.
0.05-0.06	Relaxation and Warmth. Reduced fear response. Increased reaction time. Decreased fine muscle coordination.
0.08-0.09	Impaired balance, speech, vision, hearing, muscle coordination. Euphoria.
0.14-0.15	Gross impairment of physical and mental control.
0.20-0.30	Severely intoxicated. Very little control of mind or body.
0.40-0.50	Unconscious. Deep coma. Death from respiratory depression

Ethanol [EtOH] interactions with synthesis and storage of neurotransmitter

- EtOH exposure may lead to changes in transmitter synthesis and storage
- Many of these effects are related to neurons' adaptive responses to chronic ethanol exposure (tolerance and dependence), and may not be directly involved in the acute effects of ethanol

Tolerance: Definitions

- **Tolerance: The phenomenon of decreased effect with prolonged exposure to a drug**
- **Acute tolerance: during the time-course of a single exposure to drug**
- **Chronic tolerance: over repeated use of drug**

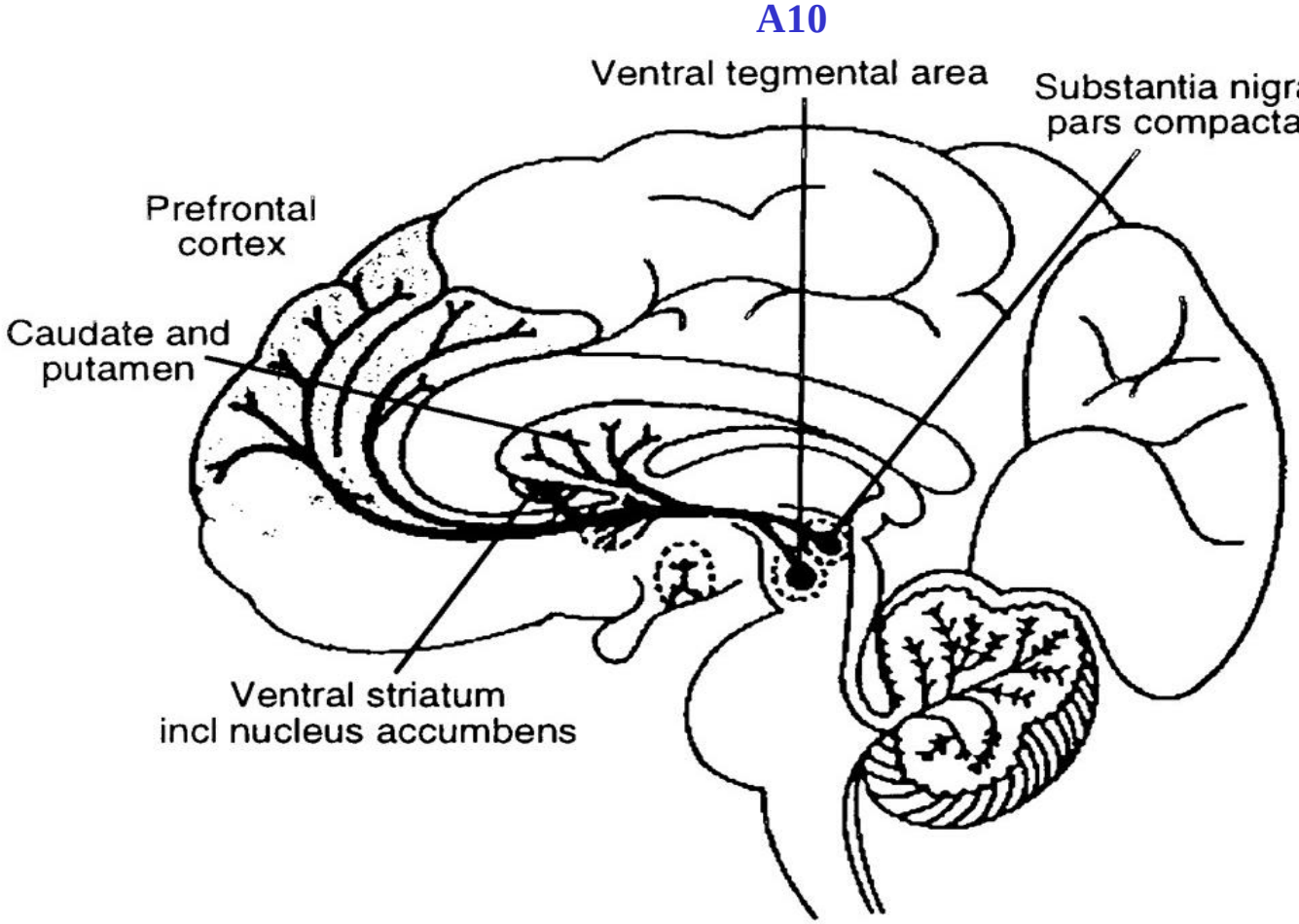
Tolerance: Significance

- **Why is tolerance to alcohol important?**
  - **One of the determinants of increased alcohol consumption**
    - **maintains or aggravates alcohol dependence**
    - **increases risk of organic complications of alcoholism**
  - **Diagnostic criteria for alcoholism by DSM-IV**
  - **Cross-tolerance to other CNS depressant drugs**
  - **Genetic determinants exist**
  - **Low Response predicts alcoholism**

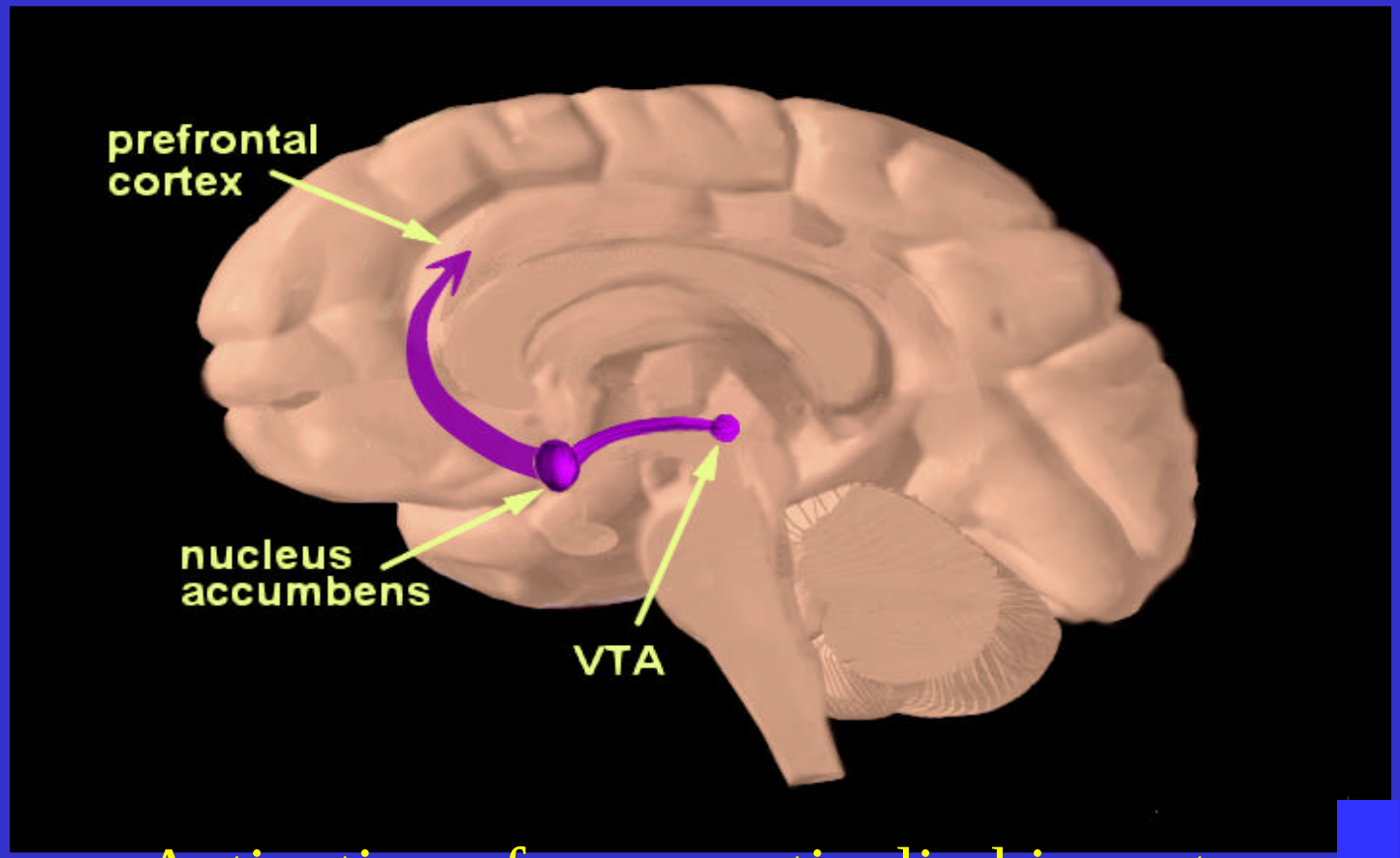
Alcohol as a Reinforcer

- **Reinforcer: a manipulation that increases the chance that the person [or animal] will perform a specific behavior**
- **Reinforcing substance: a substance whose use increases the performance of a specific behavior, such as use of the substance.**
- **Basis: pharmacological effects, social effects of substance use**
- **Positive reinforcing effects:**
  - **Increased pleasure**
  - **Altered consciousness**
  - **Acceptance or admiration by peers**
- **Negative reinforcing effects:**
  - **Relief of stress and negative emotions such as fear, sadness, & loneliness**
  - **Relief of withdrawal symptoms**

MIDBRAIN DA [REINFORCEMENT] PROJECTION PATHS
[aka mesocorticolimbic dopamine pathways]



Alcohol as a Reinforcer: Neural Systems

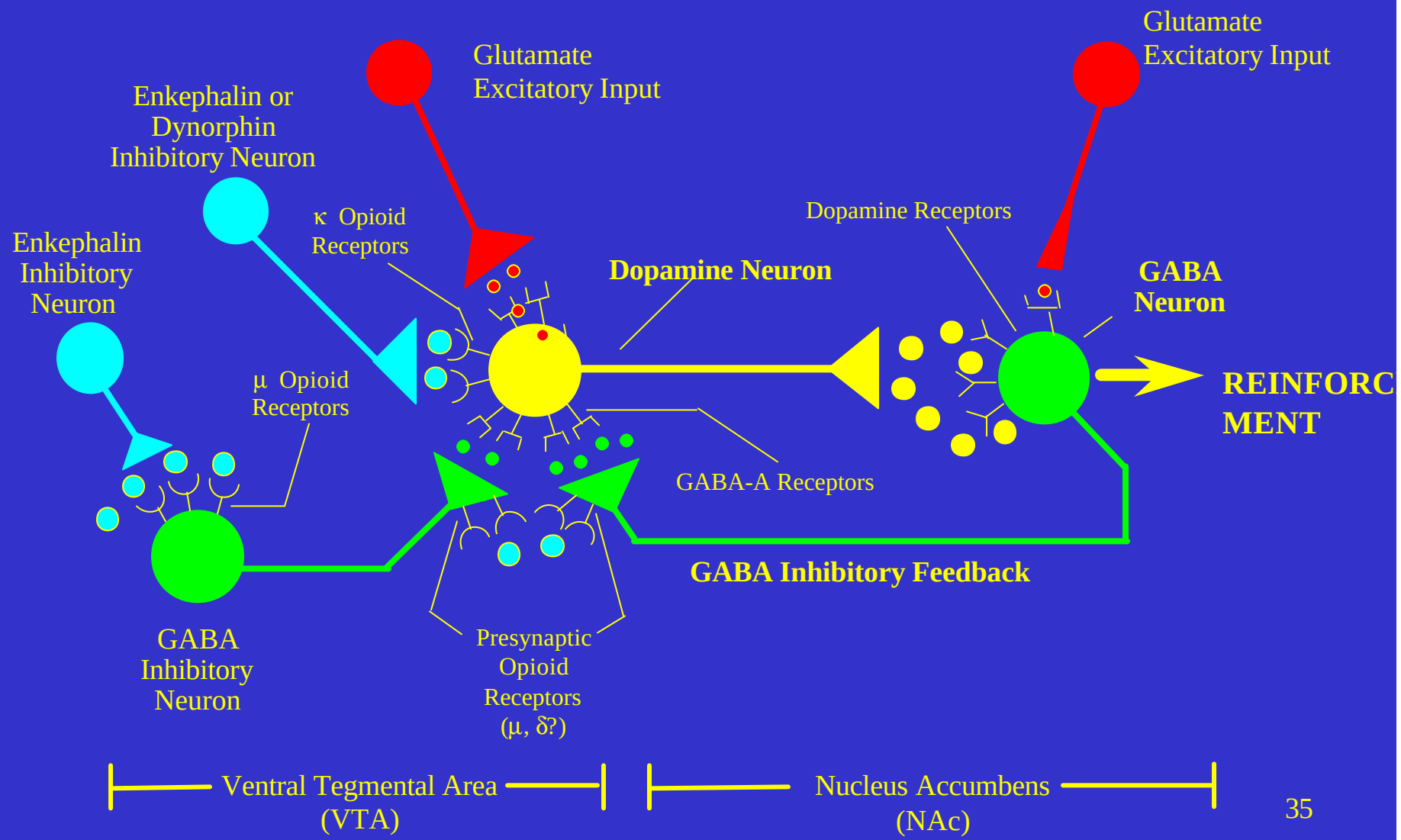


Activation of mesocorticolimbic system

Alcohol as a Reinforcer: Evidence

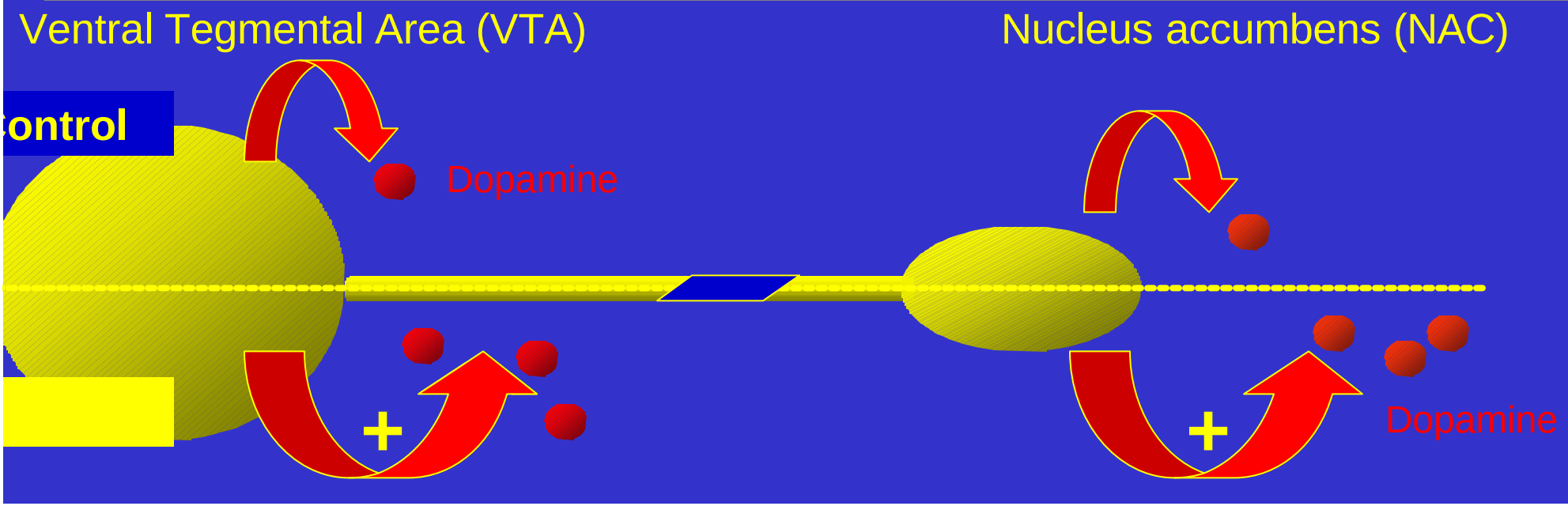
- **Animal models of alcohol preference**
  - **Selectively bred animal lines show innate differences in alcohol preference, limbic structures and neurotransmitter function**
- **Animal models of self-administration**
  - **Animals trained to chronically self-administer alcohol show differences in neurotransmitter levels in the mesolimbic DA system**
  - **Animals will bar-press repeatedly for intra-cranial injections of alcohol into the VTA**

Reinforcement: Neurochemical systems



Ethanol interactions with neurotransmitter release

- Ethanol enhances dopamine release in the “pharmacological reinforcement” pathway ; EtOH yields DA increases 200-250% over baseline
- Ethanol appears to release dopamine from the VTA and NAC via interactions with multiple neurotransmitter receptors, especially opiate receptors
- Ethanol has direct excitatory actions on dopamine containing neurons in the VTA



Ethanol interactions with neurotransmitter transporters

- **Adenosine transporter**
  EtOH inhibits adenosine transport through a specific subtype of adenosine transporter

- **Other transporters**

  Norepinephrine transporter - inhibited by ethanol
  Dopamine transporter – facilitated by ethanol
  Serotonin transporter - facilitated by ethanol

Ethanol interactions with neurotransmitter receptors (post-synaptic effects)

Synapses have 2 kinds of postsynaptic receptors

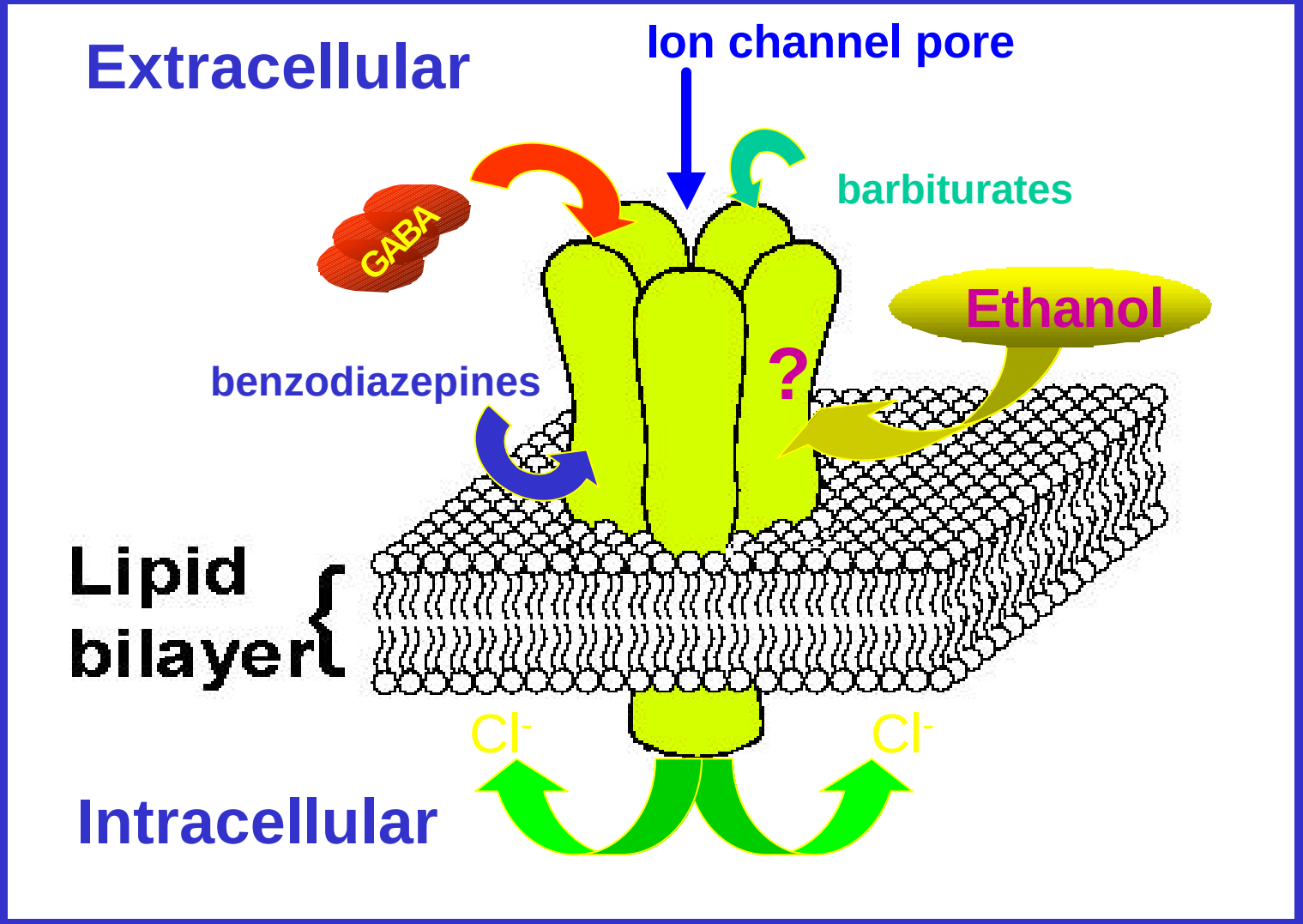
- **Ligand-gated ion channels (fast transmission, single firing)**

glutamate	$GABA_A$
glycine	acetylcholine (nicotinic)

- **Metabotropic receptors (slow transmission, modulation of firing rate)**

norepinephrine	dopamine
$GABA_B$	acetylcholine (muscarinic)
serotonin	purinergic (adenosine)

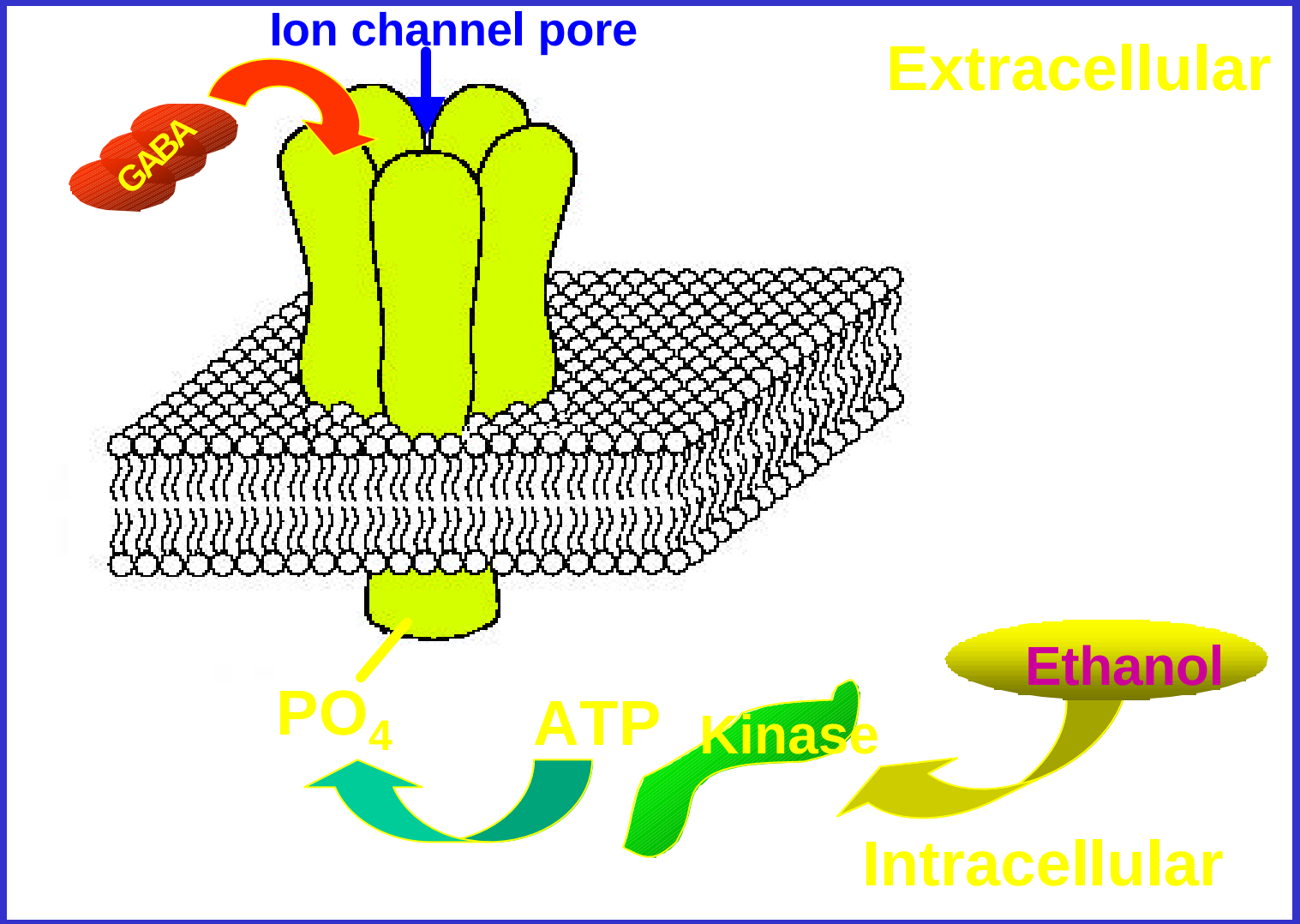
Ligand-gated ion channels: enhancement by altering channel shape



Direct interactions of ethanol with ligand-gated ion channels: allosteric enhancement

- Ethanol can potentiate the effects of some neurotransmitters on their postsynaptic receptors, e.g, 5-HT, glycine, antihistamines
- Synaptic responses are often larger in amplitude, or longer in duration
- Ethanol acts similarly to other kinds of pharmacological agents known as allosteric modulators, e.g., benzodiazepines

One possible mechanism for an indirect interaction of ethanol with a ligand-gated ion channel



Indirect interactions of ethanol with ligand-gated ion channels

- **Indirect actions mediated via kinases**
  - **Fyn-kinase - NMDA receptors**
  - **PKCγ and PKCε - $GABA_A$ receptors**
  - **Protein kinase A - $GABA_A$ receptors**
  - **Translocation of kinases (PKA/PKC)**
- **Neurosteroid mediation of ethanol effects**
  - **$GABA_A$ receptors**

Interactions of ethanol with other cellular targets

- Metabotropic (G protein coupled) receptors: interactions could be at the level of the receptor, or at the level of the transduction mechanism
  (e.g., G proteins, adenylyl cyclase)
- Many effects of ethanol have been described that seem unlikely to be mediated via effects on postsynaptic receptors, but may affect synaptic transmission
  (e.g., voltage gated ion channels)

Neuropharmacology: GABA

- Gamma amino butyric acid [GABA] is most common inhibitory neurotransmitter in the cortex, subcortex, and spinal cord
- Specific A & B receptors on nerve cells for GABA: A in brain, B in spinal cord
- Effects of ethanol on GABA system
  - Interaction with GABA-A receptor and facilitation of GABA transmission, coupled with chloride ion channel
    - Sedative and anxiolytic effects
    - Withdrawal

Neuropharmacology: DA, Opioids

- Effects of ethanol on dopamine [DA] system
  - Increase dopamine in mesocorticolimbic system
    - Reinforcing, rewarding effects
- Effects of ethanol on Opioid peptide system
  - Activation of opioid peptide system, primarily by facilitating release of endorphin and enkephalin that bind to mu and delta opiate receptors
    - Reinforcing and rewarding effects (mu and delta)
    - Aversion (kappa)
    - Craving

Neuropharmacology: NMDA, 5HT

- Glutamate, an amino acid, is primary excitatory transmitter in cortex and some subcortical areas
- Effects of alcohol on glutamate system
  - Binds, changes shape of and thus blocks NMDA type of glutamate receptor (allosteric effect)
    - Sedative/hypnotic effects
    - Memory consolidation [neuroadaptation] effects
    - Withdrawal
- Effects on serotonin [5-hydroxytryptamine, or 5-HT] system
    - Neuroadaptation, aversion
- Effects on brain stress hormones [CRH]
    - Stress response

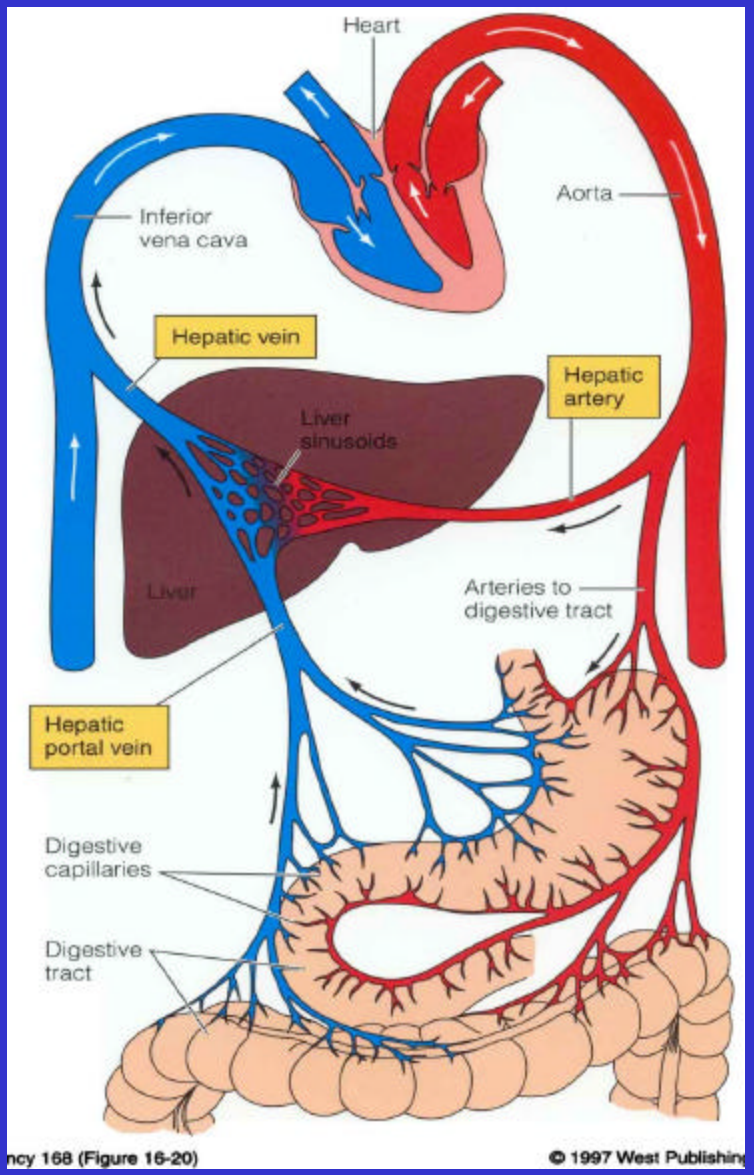
EtOH Neuropharmacology: Summary

Experience	Transmitter/Receptor
euphoria/pleasure	Dopamine, Opioids
anxiolysis/ataxia	- GABA
sedation/amnesia	- GABA + ¯ NMDA
nausea	$5HT_3$
neuroadaptation	NMDA, 5HT
stress	CRH
withdrawal	GABA, NMDA (- Ca, ¯Mg)

Implications for Pharmacotherapy

- **Disulfiram: blocks ALDH, making alcohol aversive**
- **Naltrexone: blocks mu & delta, making alcohol non-rewarding**
- **Acamprosate: blocks NMDA, making alcohol-related reinforcement learning less efficient**
- **Benzodiazepines: activate GABA, reducing withdrawal and anxiety**
- **SSRIs: block 5-HT receptors, reducing anxiety and motivation to drink**

The Liver: SIDE EFFECTS



Acute excess:

- **Acidosis**
- **Hypoglycemia**

(Multi-vitamins and carbs before bed; B-vitamins and anti-oxidants)

Chronic excess:

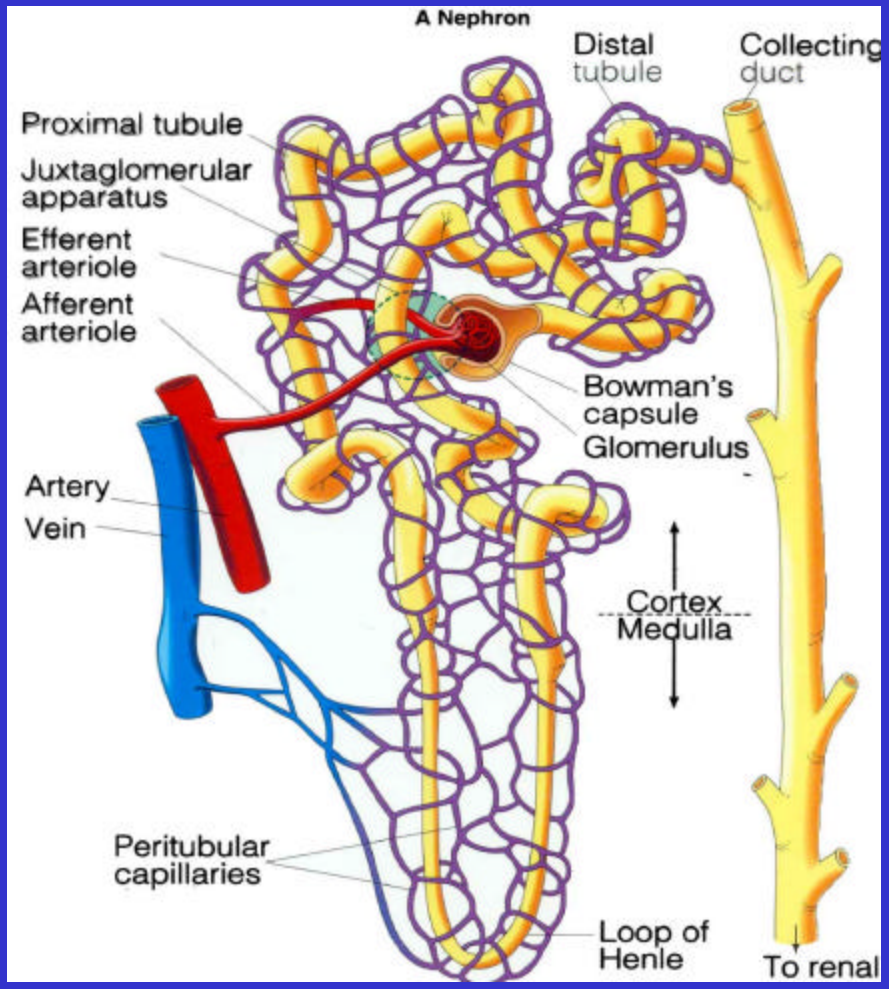
- **Hepatitis**
- **Fatty liver**
- **Cirrhosis (scarring)**
- **“Freshman 15”?**
- **Malnutrition**

Urinary System

ADH makes the kidney save water.

Side Effects:

- **Alcohol inhibits Ca2+ channels in the brain that cause ADH release.**
- **Major water loss!**
- **Electrolyte flush (Na,K)**
- **Low Blood Pressure**



Urinary System

1. When you're thirsty, it's NOT "Miller time"

2. Beer and pretzels are a great team
   (Salt drives water reabsorption without ADH)

3. The morning after:
   -saltines and water
   -chicken soup
   -sports drink (Na,K, glucose)

Cardiovascular System

Low doses seem to be good for you…..

"Moderate Consumption"

Females, 1 drink or less per day

Males, 2 drinks or less per day

Effects:

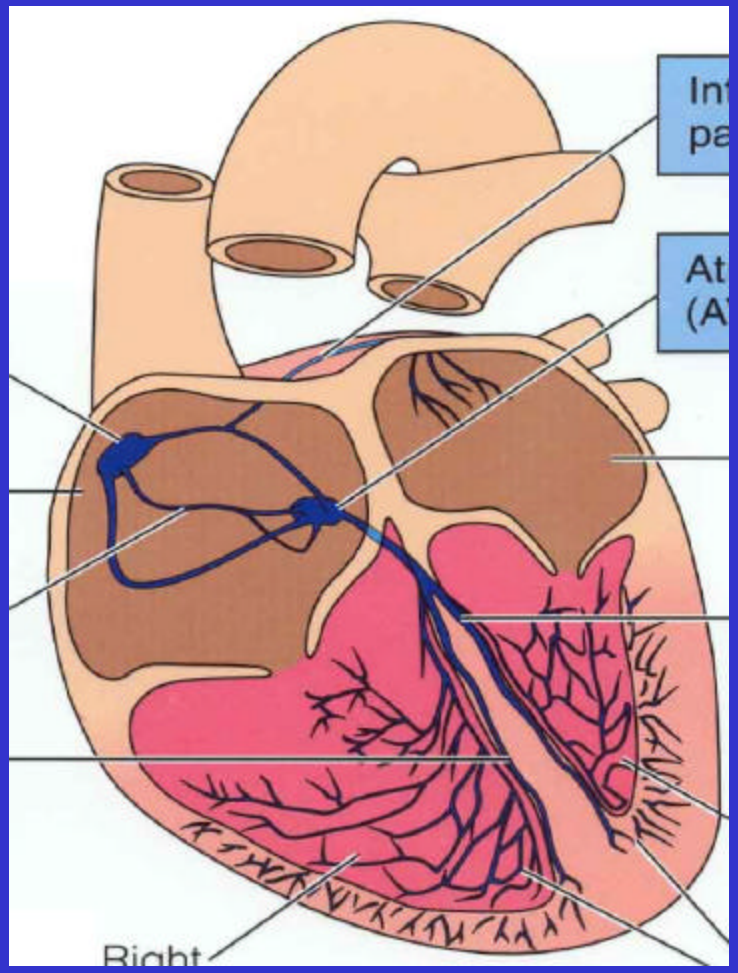
1. **Better Cholesterol profile**
   Increase HDL, Decrease LDL
2. **Reduce clotting (less stroke, heart attack)**
3. **Decrease blood pressure**
   (vasodilation, less cardiac work)

"The French Paradox"

Cardiovascular System

Heavy-Consumption:

Acute Side Effect—Arrhythmias (on Rebound)



1. Direct effect on ion channels (esp. Na+, Ca2+)

2. Loss of Na+ and K+ in excess urination

3. “Holiday heart”

Cardiovascular System

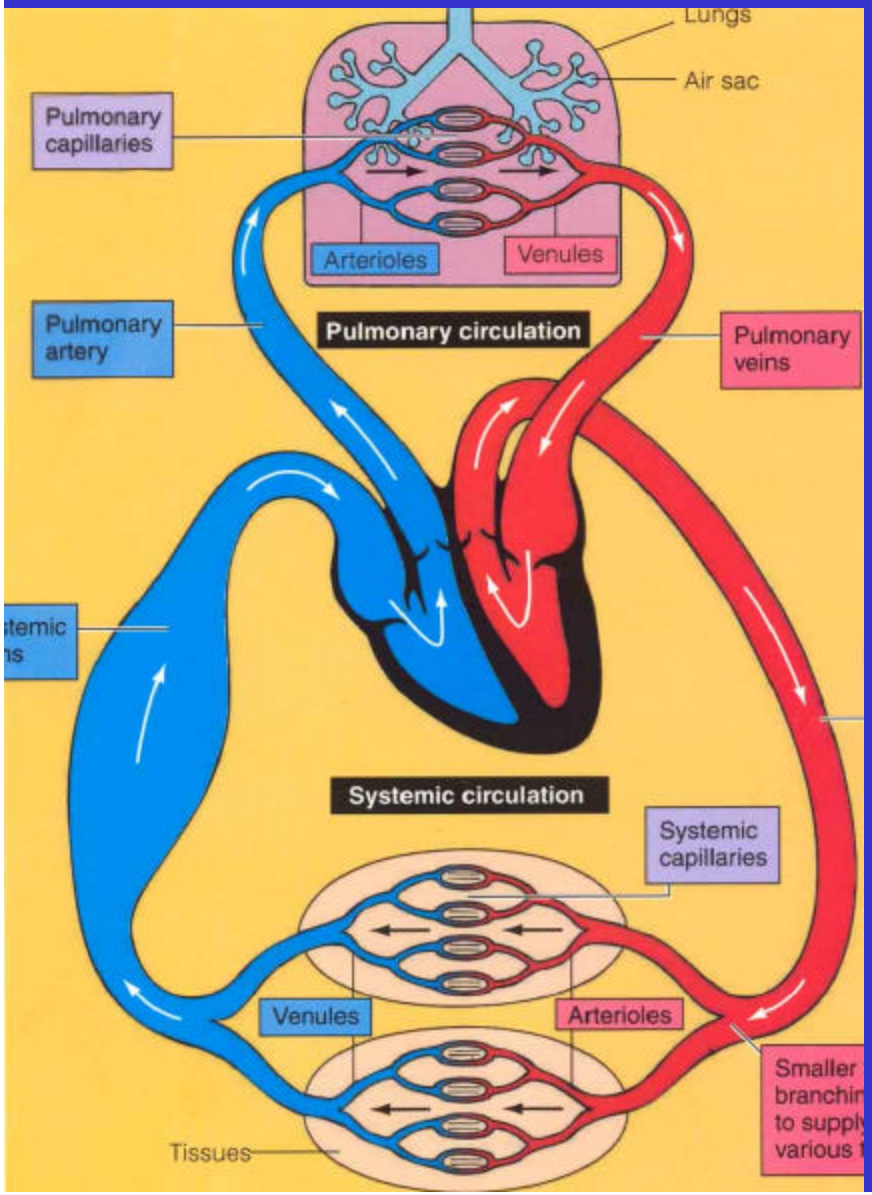
Acute Side Effect—Sexual impotence

Decreased nerve activity that normally causes vasodilation/erection

(Also impaired sensory nerve firing)

Cardiovascular System

Chronic Heavy Consumption



Side Effects:

1. Hypertension
   - -Rebound constriction of blood vessels
   - -Disruption of nerves that relax the heart
2. Heart failure
3). Stroke

Nervous System

Many Neurotransmitter Systems Implicated:
Glutamate, GABA, Dopamine, Serotonin, Acetylcholine, Endorphins, Glycine, Adenosine

General Effects/Side Effects (some disputed):

- -Depression of nerve networks
- -Decreased cognition
- -Stim. of pleasure centers
- -Decreased anxiety
- -Depression
- -Impaired judgement
- -Seizure (rebound)
- -Addiction

Nervous System

Side Effect: Acute Memory Impairment

- **-Decrease glutamate action on NMDA recpt.**
- **-Inability to strengthen synapses**
- **-Even at LOW doses**

- **-NEVER DRINK WHILE STUDYING!!!!**

Nervous System

Side Effect: Loss of Motor Coordination

Cortical and Spinal Motor Output Depressed

8th Cranial Nerve Impairment

-Decreased balance/equilibrium
-Nystagmus
-Decreased auditory sensitivity
(*"Dude, turn it up!"*)

Nervous System

Side Effect: Decreased REM sleep

-Don’t know why or how we sleep
-REM (rapid eye movement sleep) is essential
-Ethanol prevents REM

DON’T USE ETHANOL AS A SLEEP AID; IT KNOCKS YOU OUT; BUT SLEEP QUALITY IS POOR, AND REBOUND WAKES YOU UP

Summary

- **Pharmacokinetics:**
  - **Absorption depends on dose, competing food, rate**
  - **Distribution depends on tissue H_2O, blood flow; age effects**
  - **Metabolism in liver via ADH-ALDH, catalase, CYP2E1; genetic effects**
- **Pharmacodynamics:**
  - **no specific receptor but alters release and action at other receptor sites [GABA, glutamate, 5HT, etc.]**
  - **Concentration dependent effects on cerebellum, cortex, etc.**
  - **Tolerance mostly CNS**
  - **Use reinforces drinking activity via DA paths**
  - **Toxicity to multiple organs: liver, cardiac-vascular, CNS**